allowance. Applicants respectfully request favorable reconsideration and allowance.

Acknowledgement by the PTO of the receipt of applicants' papers filed under Section 119 is noted.

Applicants respectfully note that it would be considered that an error appears in the IDS filed September 3, 2002, in that it states at the bottom of page 1 that it (the IDS) was filed before the mailing date of a first Office Action on the merits. Undersigned explains that the IDS of September 3, 2002, was prepared and filed before the Office Action of August 23, 2002, reached the desk of any attorney in the office of undersigned. Applicants respectfully request the PTO to give consideration to the IDS filed September 3, 2002, particularly in that such Office Action of August 23, 2002, was vacated.

Applicants appreciate the remailing of the Office Action with a Form PTO-892 attached thereto. However, the Form PTO-948 does not list one citation which was listed in Category Y in the International Search Report, namely EP 221277; however, this document is equivalent to the cited U.S. patent 4,693,892. Attached is an English translation of what applicants deem to be a relevant portion of Fuso (JP-

D1 1157911A), as well as an English translation of the Parke Davis citation (JP-55 141242 A). D5

Applicants note that the PTO has not checked the specification to the extent necessary to determine the presence of all possible minor error. Applicants are unaware of any errors. However, if applicants notice any such errors, applicants will be sure to inform the PTO.

Claims 1 and 6 have been rejected under §102 as anticipated by Fuso. This rejection is respectfully traversed.

Claim 1 has been amended to incorporate the subject matter of claim 3. As claim 3 was not rejected as anticipated by Fuso, applicants understand that the rejection based on §102 is no longer applicable to claims 1 and 6.

Claims 1, 3 and 6 have been rejected as obvious under §103 from Fuso in view of Hegasy et al USP 4,693,892 (Hegasy). This rejection is respectfully traversed.

The present invention is based on the unobvious discovery that the incorporation of titanium oxide in the capsule shell containing iron oxide, particularly red iron oxide, serves to reduce degradation of active vitamin $D_3$ within the soft capsule shell, although the mechanism by which this unobvious improvement results is not clear. The existence of

the problem solved by the present invention is succinctly explained in the paragraph spanning pages 3 and 4 of applicants' specification as follows:

> A soft capsule formulation using iron oxide is described in JPA No. 84023/1979, which discloses a soft capsule formulation of an active vitamin $D_3$ encapsulated with a shell containing yellow iron oxide and red iron oxide, but it is reported to be insufficient in stability to heat. A method for preventing destabilization of active ingredients due to direct contact of the active ingredients with red iron oxide (diiron trioxide) in soft capsule shells is reported by JPA No. 157911/1989, which discloses a light-screening capsule formulation wherein microencapsulated red iron oxide is dispersed in a shell to prevent direct contact of red iron oxide with the drug in the capsule, but this method is not a practical means of production since it requires complex operations such as the preparation of microcapsules containing red iron oxide.

The question thus arose as to how to more simply provide a soft capsule shell containing iron oxide which maintains heat and light stability of the active vitamin $D_3$ therewithin without going to the complex mechanisms of the prior art, and without including organic UV absorbers and dyes which have questionable safety.

All of applicants' examples in the present specification are based on the use of titanium oxide, except of course for the comparative examples. Attention is respectfully invited particularly to the test examples,

commencing near the bottom of page 16, which demonstrate the improved results according to the present invention, and especially table 3 at the top of page 18 which shows that comparative example 1, wherein the shell of the soft capsule did not contain titanium oxide, resulted in very substantial degradation of the vitamin $D_3$.

Test example 2, pages 18 and 19, noting especially table 4 wherein a comparison is provided between example 6 and comparative example 3, shows even more dramatic results. Incidentally, comparative examples 2 and 4 in tables 3 and 4, respectively, may be disregarded because those comparative examples did contain titanium oxide, but no iron oxide.

The primary reference relied upon is Fuso, the inventors of which faced the same or similar problem faced by the present applicants. Fuso, however, teaches a much more complex (and therefore difficult and costly) solution to the problem, namely the **encapsulation** of the red iron oxide. **Indeed, it is the Fuso disclosure which is referred to in applicants' specification at the top of page 4, quoted above as JPA No. 157911/1989.** This complex solution proposed by Fuso can also be readily seen from the attached English translation of Fuso. To briefly reiterate, Fuso encapsulated red iron oxide in microcapsules to avoid direct contact between active ingredients and the red iron oxide.

Contrary to Fuso, according to the instant invention the stability of active ingredients increases by mixing red iron oxide and titanium oxide into the capsule shells, without encapsulating the red iron oxide at all. Thus, whereas the person of ordinary skill in the art would expect from Fuso that applicants' approach would not work because the iron oxide must be isolated, in fact the present invention does work, and these results could not have been predicted or foreseen from the prior art, i.e. such results are unobvious. From a consideration of Fuso, there would have been no reasonable expectation that success could be achieved by eliminating the microencapsulating taught by Fuso as being essential, and indeed such success seems most unlikely from Fuso.

The rejection states that Fuso does not teach titanium dioxide, and therefore relies on Hegasy, it being the position of the PTO that it would have been obvious to the person of ordinary skill in the art, at the time the present invention was made, to either add titanium oxide to the capsule composition of Fuso, or possibly substitute the titanium oxide of Hegasy for the calcium carbonate of Fuso. **However, even if such an expedient were obvious, the resultant combination would still involve the encapsulation of the iron oxide!** Applicants' invention would not be achieved, because

the person skilled in the art following Fuso as a primary reference would do as Fuso requires, i.e. encapsulate the iron oxide.

Actually, Hegasy adds nothing to Fuso. In this regard, the rejection is incorrect in its implication that Fuso does not mention titanium dioxide. In fact, Fuso describes (translation) "metal oxides, such as red iron oxide and titanium oxide, which have visually appealing color tone, excellent light-shielding effects and biological safety, have been proposed for replacing tar-based synthetic dyes". However, Fuso does not disclose the combined use of titanium oxide and red iron oxide, a main feature of the present invention.

A consideration of Fuso alone or Fuso in view of Hegasy would not have led the person of ordinary skill in the art to or toward the present invention. Even it were obvious to use titanium dioxide along with iron oxide from a consideration of Fuso alone or Fuso in view of Hegasy, respectfully not admitted by applicants, the iron oxide would still be encapsulated according to Fuso, and that would not correspond with the present invention. Moreover, the person of ordinary skill in the art would have had no reasonable expectation that the incorporation of titanium oxide with iron

oxide would provide the beneficial effects of the present invention as shown in applicants' examples.

Applicants respectfully request withdrawal of the rejection.

Claims 1 and 3-6 have been rejected as obvious under §103 from Fuso in view of Yamada et al JP 63-166824 (Yamada). This rejection is respectfully traversed.

Yamada teaches no more than Hegasy, except for the presence of glyceride ester, the presence of which is not relied upon at present by applicants for patentability. Accordingly, all the commentary made above with respect to the proposed combination of Fuso and Hegasy are equally applicable here and are respectfully repeated by reference.

Fuso not only requires that the red iron oxide be suitably encapsulated in microcapsules, but also requires the presence of an alkaline earth metal carbonate or silicate. In this regard, Fuso states as follows (translation):

> As a result of careful studies to obtain soft capsule formulations that are stable over time by protecting drugs contained therein from light, and from any oxidizing action of light-shielding inorganic materials, the inventors [Fuso et al] … have found that it is possible for red iron oxide to be suitably encapsulated in microcapsules… when such microcapsules include at least one of an alkaline earth metal carbonate or silicate…. [bracketed material added]

An alkaline earth metal carbonate is not necessary in the present invention. Fuso teaches away from the present invention, and following Fuso cannot result in the claimed subject matter.

Withdrawal of the rejection is respectfully requested.

Claims 1-3 and 9 have been rejected as obvious from Fuso in view of Sakagami JP '824 or Parke Davis JP '242. Moreover, claims 1-9 have been rejected as obvious under Section 103 from Fuso in view of Sakagami or Parke Davis, further in view of Yamada. These rejections are respectfully traversed.

Fuso and Yamada have been discussed above. Parke Davis and Sakagami are not seen to add anything further. Fundamentally missing from any combination, even assuming *ad arguendo* that such a combination were obvious, is the concept of providing a simple mixture of the components rather than going to the high cost of encapsulation which the prior art suggests is essential, and which the person of ordinary skill in the art would necessarily believe. The references, even if they were obviously combinable, do not make applicants' claims obvious.

Accordingly, applicants respectfully request withdrawal of the aforementioned rejections based on Section 103.

New claims 10-15 have been added above. These claims are patentable for the same reasons as pointed out above. The prior art does not teach a homogenous mixture of white pigment and iron oxide, let alone the unobvious effects which result therefrom.

Favorable reconsideration and allowance are earnestly solicited.

Respectfully submitted,

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Version with Markings to Show Changes Made

1. (amended) A soft capsule formulation comprising:

an oily solution of an active vitamin $D_3$; and

a soft capsule shell which contains ~~a white pigment~~titanium oxide and yellow iron oxide and/or red iron oxide and encapsulates said oily solution of an active vitamin $D_3$.

2. (amended) A soft capsule formulation comprising:

an oily solution of an active vitamin $D_3$; and

a soft capsule shell which contains ~~a white pigment~~titanium oxide and caramel and encapsulates said oily solution of active vitamin $D_3$.

**Translation of JP-A-55141242**

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1. Title of the Invention

Gelatin capsules

2. Claims

1. A colored gelatin capsule comprising caramel and a condensed phosphate, which are uniformly dispersed therein.

2. The gelatin capsule according to claim 1, wherein the amount of caramel is 0.05% to 5.0% by weight and the amount of the condensed phosphate is 0.01% to 0.1% by weight.

3. The gelatin capsule according to claim 1, which further comprises titanium dioxide.

4. The gelatin capsule according to claim 3, wherein the amount of titanium dioxide is 0.1% to 3.0% by weight.

3. Detailed Description of the Invention

The present invention relates to gelatin capsules which involve no problem with safety, have good color stability and are capable of commercial production.

Conventional capsules have been commonly colored with tar-based synthetic dyes, alone or in combination, which are listed in the Japanese Standard of Food Additives, or in combination with titanium dioxide according to the Japanese Pharmacopoeia. Such coloring was intended for the main purpose of distinguishing between capsule formulations, which can prevent misuse and is convenient for drug production, and for the secondary purpose of providing aesthetically pleasing color tones to improve the commercial value of the formulations.

Recent scientific research has discovered an increasing number of tar-based synthetic dyes with unwanted harmful effects, which has led to considerable public concern regarding the safety of such dyes in the human body.

In addition, recent attention has been focused on natural colorants commonly used in foods as alternatives to tar-based synthetic dyes. For example, caramel has been used alone or in combination with titanium dioxide at given ratios. In this case, however, the resulting capsules had clearly visible small dark brown spots. For medical use, in particular, those spots would be identified as foreign materials and generally cause a serious problem of significantly reducing the commercial value of the

capsules.

As a result of extensive and intensive efforts made to overcome this point, it has been found that the addition of a condensed phosphate successfully prevents spot formation and provides heat- and light-stable gelatin capsules which are excellent in color tone and gloss and which are suitable for commercial production scale.

Namely, the present invention relates to a colored gelatin capsule comprising caramel and a condensed phosphate, which are uniformly dispersed therein, and further comprising titanium dioxide. Preferably, the gelatin capsule comprises caramel in an amount of 0.05% to 5.0% by weight, a condensed phosphate in an amount of 0.01% to 0.1% by weight, and titanium dioxide in an amount of 0.1% to 3.0% by weight.

Caramel as mentioned above may be obtained by heat treatment of food carbohydrates, including glucose, sucrose, invertose, millet jerry, starch hydrolyzates, molasses and other sugars, in the presence or absence of a small amount of an acid, an alkali or other food additives. Such caramel is accepted as a food colorant in FAO/WHO, US and EC countries. In Japan, it is also widely used in drugs, soft drinks, confectioneries, soy sauce, etc.

A condensed phosphate is intended for use as a sequestering agent or an acidic ingredient of synthetic baking powders in the

food industry, and it can be found in the third edition of the Japanese Standard of Food Additives. Such a condensed phosphate has the chemical formula $M_{n+2}P_nO_{3n+1}$ or $(MPO_3)_n$ (wherein M represents an alkali metal such as sodium or potassium, and n represents the degree of condensation) and examples include, but are not limited to, sodium pyrophosphate, sodium polyphosphate, potassium polyphosphate and sodium metaphosphate. Any other condensed phosphate may also be used.

As for titanium dioxide, it is sufficient for this purpose to use fine powders of pharmacopeial grade titanium dioxide as defined in the Japanese Pharmacopoeia.

Condensed phosphates are added, alone or in combination, for the purpose of preventing spot formation during caramel coloring. Addition can be done in any order, for example, by preparing an aqueous solution of a condensed phosphate and caramel and then adding this solution to a gelatin stock solution for gelatin capsule preparation, by adding a condensed phosphate to a gelatin solution colored with caramel, or by adding caramel to a gelatin solution supplemented with a condensed phosphate.

Likewise, in the case of adding titanium dioxide, addition may be done in any order as long as titanium dioxide can be uniformly dispersed in a gelatin stock solution, for example, by adding caramel and a condensed phosphate to a gelatin solution comprising titanium dioxide uniformly dispersed therein or by

dispersing titanium dioxide into a gelatin solution colored with caramel and a condensed phosphate.

The gelatin solution as used here may be prepared by dissolving gelatin in boiling water and, if necessary, adding a preservative. This gelatin solution will have a concentration of around 35% by weight and a viscosity of 800 to 1000 cps (at 45°C). For uniform dispersion, there is no need to use any particular equipment and it is sufficient to use known apparatuses and methods to obtain aesthetically pleasing capsules.

In addition, caramel can be successful for the purpose of coloring even in the presence of plasticizers, preservatives, dispersants and other additives necessary for machine production of gelatin capsules.

Further, the capsules thus formed have a brown tone, which is stable to temperature and light.

Also, the tone of the capsules can be continuously varied by adjusting the amounts of caramel and titanium dioxide used.

The term "gelatin capsule" as used herein is intended to have the same meaning as capsule (Capsulae Operculatae) as defined in the Japanese Pharmacopoeia, 9th edition.

Namely, caramel-colored capsules supplemented with a condensed phosphate involve no problem with safety and meet the capsule quality defined in the Japanese Pharmacopoeia (i.e.,

appearance properties and purity test); they also show exactly the same disintegration as conventional capsules, as tested by General Tests, Process and Apparatus No. 33 disintegration test. Such capsules are therefore available for pharmaceutical or food use.

The present invention will be further described in the following Examples and Comparative Examples, which are not intended to limit the scope of the invention.

Example 1

Gelatin was dissolved in boiling water to prepare a gelatin solution with a concentration of about 35% by weight and a viscosity of 900 cps (at 45°C). To this gelatin solution, aqueous solutions of caramel and a condensed phosphate were added and mixed uniformly. The respective amounts of caramel and the condensed phosphate added to gelatin are as shown in Table 1. This mixture was used to prepare hard gelatin capsules in a general manner. The resulting capsules have various non-spotted good tones of transparent brown, which vary depending on the amount of caramel incorporated.

Table 1 Stability

| Condensed phosphate (wt%) | | Caramel (wt%) | 40°C × 40%RH × 4 weeks | 2.5KW Xenon lump × 6 hours |
|---|---|---|---|---|
| Sodium pyrophosphate (anhydride) | 0.01 | 0.5 | No change | No change |
| | 0.03 | 1.0 | 〃 | 〃 |
| | 0.10 | 3.0 | 〃 | 〃 |
| Sodium metaphosphate | 0.01 | 0.5 | 〃 | 〃 |
| | 0.03 | 1.0 | 〃 | 〃 |
| | 0.10 | 3.0 | 〃 | 〃 |
| Sodium polyphosphate | 0.01 | 0.5 | 〃 | 〃 |
| | 0.03 | 1.0 | 〃 | 〃 |
| | 0.10 | 3.0 | 〃 | 〃 |

Caramel: Anstead, grade #13923

Condensed phosphate: Taihei Chemical Industrial Co., Ltd.

As shown in Table 1, capsules colored with caramel and condensed phosphates are highly stable over time and light exposure, etc.

Example 2

Titanium dioxide was uniformly mixed in water to prepare capsules colored with caramel and condensed phosphates in the same manner as shown in Example 1. The respective amounts of caramel, a condensed phosphate and titanium dioxide added are as shown in Table 2. The resulting capsules have various non-spotted good tones of opaque brown.

Table 2 Stability

| Condensed phosphate (wt%) | | Caramel (wt%) | Titanium dioxide (wt%) | 40°C × 40%RH × 4 weeks | 2.5KW Xenon lump × 6 hours |
|---|---|---|---|---|---|
| Sodium pyrophosphate (anhydride) | 0.01 | 0.5 | 1.5 | No change | No change |
| | 0.03 | 1.0 | 1.5 | 〃 | 〃 |
| | 0.10 | 3.0 | 1.5 | 〃 | 〃 |
| Sodium metaphosphate | 0.01 | 0.5 | 1.5 | 〃 | 〃 |
| | 0.03 | 1.0 | 1.5 | 〃 | 〃 |
| | 0.10 | 3.0 | 1.5 | 〃 | 〃 |
| Sodium polyphosphate | 0.01 | 0.5 | 1.5 | 〃 | 〃 |
| | 0.03 | 1.0 | 1.5 | 〃 | 〃 |
| | 0.10 | 3.0 | 1.5 | 〃 | 〃 |

Caramel: Anstead, grade #13923

Condensed phosphate: Taihei Chemical Industrial Co., Ltd.

As shown in Table 2, capsules colored with caramel, condensed phosphates and titanium dioxide are highly stable over time and light exposure, etc.

Comparative Example 1

Capsules colored with caramel alone were formed in the absence of a condensed phosphate. The amount of caramel added to gelatin is as shown in Table 3. The resulting capsules had various tones of transparent brown along with visible spots, resulting in significantly reduced commercial value.

Table 3 Spot counts

| Caramel (wt%) | Spot counts (per 300 capsules of size #1) |
|---|---|
| 0.5 | 0 |
| 1.0 | 0 |
| 3.0 | 4 |

Caramel: Anstead, grade #13923

As shown in Table 3, in the absence of a condensed phosphate, spots were observed in capsules colored with 3.0% by weight of caramel.

Comparative Example 2

Titanium dioxide was uniformly mixed to prepare capsules colored with caramel in the same manner as shown in Comparative Example 1. The respective amounts of caramel and titanium dioxide added are as shown in Table 4. The resulting capsules had various tones of opaque brown along with visible spots, resulting in significantly reduced commercial value.

Table 4 Spot counts

| Caramel (wt%) | Titanium dioxide (wt%) | Spot counts (per 300 capsules of size #1) |
|---|---|---|
| 0.5 | 1.5 | 6 |
| 1.0 | 1.5 | 7 |
| 3.0 | 1.5 | 26 |

Caramel: Anstead, grade #13923

As shown in Table 4, in the absence of a condensed phosphate, spots were observed in capsules colored with as little as 0.5% by weight of caramel. Spot counts increased in proportion to the amount of caramel.

English Translation of JP 1-157911 A (from line 9 of the right column of page 77 to line 2 of the left lower column of page 78)

[Prior art and problems]

For capsule formulations having active ingredients (e.g., drugs) encapsulated in capsule shells, coloring materials are conventionally added to the capsule shells in order to prevent accidental misuse or photodegradation of the active ingredients. In the case of vitamin (especially vitamin $D_3$) capsule formulations which require light-shielding, light non-transmitting materials are contained in capsule shells to prevent light reaching and degrading the active ingredients. Such light non-transmitting materials are also utilized to enable visual discrimination of amounts of an active ingredient in formulations, so that formulations containing differing amounts of an active ingredient can be appropriately used depending on a disease to be treated, or age or condition of a patient at a time of treatment.

Soft capsule formulations are produced such that active ingredients with or without the use of suitable excipients are encapsulated in gelatin capsule shells the plasticity of which shells is increased by adding glycerin, sorbitol, etc. When formulating a highly bioactive drug (e.g., vitamin D, and particularly vitamin $D_3$), an extremely small amount of a drug is required to be encapsulated uniformly. To properly encapsulate such a drug in a soft capsule formulation, it is indispensable to uniformly disperse the drug in a liquid material such as an oily base. Some attempts have been made to color capsule shells of such capsule formulations by adding tar-based

synthetic dyes for the purpose of discrimination and prevention of light-degradation. However, the safety of such tar-based synthetic dyes has recently been questioned, and tar-based synthetic dyes are thus undesirable for use in medicaments to be administrated to human bodies.

Accordingly, metal oxides (such as red iron oxide and titanium oxide), which have visually appealing color tones, excellent light-shielding effects and biological safety, have been proposed as replacements for tar-based synthetic dyes (JP 57-4345 B). However, in dispersing red iron oxide in soft capsule shells it comes into direct contact with the active ingredients, and as a result of its oxidizing action causes the active ingredients to become unstable, and to readily become inactivated by, for example, heat. One approach to overcoming this problem may be to disperse in soft capsule shells red iron oxide encapsulated in microcapsules, to thereby avoid contact between the red iron oxide and the contained drugs. However, it has been found that since water soluble gelatins are generally used as coating materials of microcapsules, the coating of the microcapsules and the capsule shells melt together under a forming process using heat, resulting in destruction of a microcapsule structure.

[Means for solving the problems]

As a result of careful studies to obtain soft capsule formulations that are stable over time by protecting drugs contained therein from light, and from any oxidizing action of light-shielding inorganic materials, the inventors of the present invention have found that it is possible for red iron oxide to be suitably encapsulated in microcapsules and then uniformly dispersed in gelatin capsule shells when such microcapsules include at least one of an alkaline earth metal carbonate or silicate as a coating material,

and further that such capsule formulations are light-shielding as well as being able to prevent an oxidizing action of red iron oxide.